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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/811,170	03/26/2004	Mark W. Sleeman	REG 711A	2033

26693 7590 10/31/2005

REGENERON PHARMACEUTICALS, INC
777 OLD SAW MILL RIVER ROAD
TARRYTOWN, NY 10591

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 10/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/811,170	SLEEMAN ET AL.	
	Examiner	Art Unit	
	Jon M. Lockard	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,8-10,13-15,18,19,25 and 26* is/are pending in the application.

4a) Of the above claim(s) *25 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,8-10,13-15,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,6,8-10,13-15,18,19,25 and 26* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/26/04, 11/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II, claims 2-5, 6, 8, 10-14, and 16-21 and the elected species of VEGFR1R2-FcΔC1, in so far as they are drawn to a method for treating diabetes by administering VEGFR1R2-FcΔC1, in the reply filed on 25 July 2005 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP §818.03(a)).

2. It is noted that newly added claims 25 and 26 are drawn to a non-elected invention, and therefore have been withdrawn from further consideration. The basis for this restriction requirement was set forth for claims 22-23 (Groups VII and VIII) at pages 5-6 of the Restriction Requirement (mailed 18 July 2005). Therefore, claims 25-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 25 July 2005.

3. The restriction requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

4. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Jon Lockard.

5. The Amendment filed 25 July 2005 has been received and entered in full. Claims 1, 6, 9, 13, and 15 have been amended, claims 3-5, 7, 11-12, 16-17, and 20-24 have been cancelled, and

claims 25-26 have been added. Therefore, claims 1-2, 6, 8-10, 13-15, 18-19, and 25-26 are pending, claims 25-26 are withdrawn from further consideration as discussed above, and claims 1-2, 6, 8-10, 13-15, and 18-19, in so far as they are drawn to a method for treating diabetes by administering VEGFR1R2-FcΔC1 are the subject of this Office Action.

Information Disclosure Statement

6. The Information Disclosure Statements (IDS) submitted on 26 March 2004 and 15 November 2004 have been considered by the Examiner.

Specification

7. The disclosure is objected to because of the following informalities

8. The use of the trademarks has been noted throughout the Specification (See page 10 [0045], for example). Trademarks should be capitalized wherever they appear and should be accompanied by the generic terminology. Applicant is encouraged to review and make appropriate corrections to the specification regarding the misuse of trademarks. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Objections

9. Claims 6, 13, and 18 are objected to because of the following informalities.

10. Claims 6, 13, and 18 are objected to for encompassing a non-elected inventions, e.g., Flt-1(1-3)-Fc, Flt-1(1-$3_{R>N}$)-Fc, etc...

Appropriate correction is suggested.

Claim Rejections - 35 USC § 112, 1st Paragraph (Scope of Enablement)

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-2, 8, 9-10, 14, 15, and 19 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of treating or inhibiting the progression of non-insulin dependent (Type 2) diabetes mellitus (NIDDM) or improving glucose tolerance or insulin sensitivity in a human subject in need thereof comprising administering a VEGF antagonist, wherein the VEGF antagonist is VEGFR1R2-FcΔC1, does not reasonably provide enablement for a method of treating or inhibiting the progression of non-insulin dependent (Type 2) diabetes mellitus (NIDDM) or improving glucose tolerance or insulin sensitivity in a human subject in need thereof comprising administering any VEGF antagonist; a method for inhibiting the development of non-insulin dependent (Type 2) diabetes mellitus (NIDDM) in a human subject suffering therefrom; or a method for inhibiting the development or progression of non-insulin dependent (Type 2) diabetes mellitus (NIDDM) in a human subject at risk for developing type 2 diabetes. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

13. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

14. The claims are drawn very broadly to VEGF antagonists. While the specification provides the structure of 8 VEGF traps (i.e., Flt-1(1-3)-Fc, Flt-1(1-$3_{R>N}$)-Fc, Flt-1(1-$3_{\Delta B}$)-Fc, Flt1(2-$3_{\Delta B}$)-Fc, Flt-1(2-3)-Fc, Flt-1D2-VEGFR3-FcΔC1(a), Flt-1D2-Flk-1D3-FcΔC1(a), and VEGFR1R2-FcΔC1(a), it does not teach a commensurate number of the claimed species of VEGF antagonists which the specification teaches can be an antibody, lipid, nucleic acid, small molecule, aptamer, antisense molecule, carbohydrate, peptidomimetic, or hapten (See pages 1-2 [0006]). Based on the very limited number of disclosed species, it is not at all predictable what essential features are required for a compound to have the claimed property of being a VEGF antagonist, and it would require undue experimentation to determine such. As the specification does not teach how to make and use a number of species that would be commensurate in scope with the claims, it is found that it would require undue experimentation to practice the invention in a manner commensurate in scope with the claims, given the lack of guidance in the

specification and the very broad scope of the claims. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide binding/activity of the antagonist; and the breadth of the claims which fail to recite any structural or functional limitations; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. While the specification teaches that subcutaneous administration of VEGFR1R2-FcΔC1(a) in a mouse model type 2 diabetes results in decreased serum glucose concentrations, improved glucose tolerance, increased insulin sensitivity (as measured via fasting glucose levels), and reduced hyperinsulinemia (as measured via an oral glucose tolerance test), it does not teach a commensurate number of species of routes of administration that would result in treatment that are encompassed by the claims, which would include intravenous, intramuscular, oral, topical, inhalation, intraperitoneal, intradermal, and transdermal, for example.

16. The art teaches that the goal of delivering proteins and peptides noninvasively has only achieved modest success, with poor applicability to proteins and peptides (See for example Pettit et al. "The development of site-specific drug-delivery systems for protein and peptide biopharmaceuticals". Trends Biotechnol 16: 343-349, 1998; See especially pg 343, col 1-2). The problems posed by proteins and peptides is their large molecular size, electrical charge, relatively hydrophilic nature, and relative instability in environments of extreme pH or proteolytic activity (such as the stomach and intestine) (pg 343, col 2). Pettit et al. review several routes of protein administration and the limitations that have been encountered. For example, limited success has

been achieved delivering proteins and peptides orally because of: 1) poor intrinsic permeability across intestinal epithelium, 2) susceptibility to enzymatic attack, 3) rapid post-absorptive clearance, and 4) chemical instability (pg 344-345). Although much effort has been given to the transdermal delivery of pharmaceutical products, clinical applications have been limited to non-protein drugs because of the skin's poor permeability to proteins and peptides (pg 343, col 2). Additionally, proteins or peptides administered systemically must resist clearance via molecular filtration by the kidney and clearance by the reticuloendothelial system (pg 345, col 2). Therefore, the state of the prior art establishes the unpredictability of delivering proteins to a subject.

17. Since the specification only teaches the subcutaneous route of administration treats diabetes, it is not predictable that any other route of administration of VEGFR1R2-FcΔC1(a) would meet the claimed limitation of treating diabetes, and it would require undue experimentation to determine such. As the specification does not teach a number of routes of administration that would be commensurate in scope with the claims, it is found that the skilled artisan would require undue experimentation to practice the invention in a manner commensurate in scope with the claims, given the lack of guidance in the specification, the very broad scope of the claims, and the unpredictability of the art set forth above.

18. Lastly, while the specification teaches that subcutaneous administration of VEGFR1R2-FcΔC1(a) in a mouse model type 2 diabetes results in decreased serum glucose concentrations, improved glucose tolerance, increased insulin sensitivity (as measured via fasting glucose levels), and reduced hyperinsulinemia (as measured via an oral glucose tolerance test), it does not teach that administration of VEGFR1R2-FcΔC1(a) is capable of inhibiting the development

of type 2 diabetes in a human subject at risk for developing type 2 diabetes. Based on the working examples provided in the specification, it is not at all predictable, nor is there any reasonable expectation, that administration of VEGFR1R2-FcΔC1(a) would have the claimed property of inhibiting the development of type 2 diabetes in a human subject at risk for developing type 2 diabetes.

19. Thus, in view of the lack of guidance, the breadth of the claims, and the lack of working examples, the instant specification is not found to be enabling for a method for inhibiting the development of type 2 diabetes in a human subject at risk for developing type 2 diabetes comprising administering VEGFR1R2-FcΔC1(a) or a VEGF antagonist. It would require undue experimentation and making a substantial inventive contribution for the skilled artisan to discover how to use the Applicants' invention as currently claimed.

Claim Rejections - 35 USC § 112, 1st Paragraph (Written Description)

20. Claims 1-2, 8, 9-10, 14, 15, and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

21. The claims are drawn very broadly to VEGF antagonists. The claims do not set forth any essential features that are required for a compound to have the claimed property of being a VEGF antagonist.

22. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claims is a desired functional property in the form of the recitation of being an antagonist. However, there does not appear to be an adequate written description in the specification as filed of any essential structural feature common to molecules that are VEGF antagonists. The specification discloses structure of 8 VEGF traps (i.e., Flt-1(1-3)-Fc, Flt-1(1-$3_{R>N}$)-Fc, Flt-1(1-$3_{\Delta B}$)-Fc, Flt1(2-$3_{\Delta B}$)-Fc, Flt-1(2-3)-Fc, Flt-1D2-VEGFR3-FcΔC1(a), Flt-1D2-Flk-1D3-FcΔC1(a), and VEGFR1R2-FcΔC1(a). Thus, the disclosure of eight species of VEGF traps does not appear to provide an adequate written description of the extensive genus of molecules which are VEGF antagonists which the specification teaches can be an antibody, lipid, nucleic acid, small molecule, aptamer, antisense molecule, carbohydrate, peptidomimetic, or hapten (See pages 1-2 [0006]). The distinguishing characteristics of the claimed genus are not described. The only adequately described species are the VEGF traps set forth in the specification as Flt-1(1-3)-Fc, Flt-1(1-$3_{R>N}$)-Fc, Flt-1(1-$3_{\Delta B}$)-Fc, Flt1(2-$3_{\Delta B}$)-Fc, Flt-1(2-3)-Fc, Flt-1D2-VEGFR3-FcΔC1(a), Flt-1D2-Flk-1D3-FcΔC1(a), and VEGFR1R2-FcΔC1(a). Accordingly, the specification does not provide adequate written description of the claimed genus.

23. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

24. With the exception of the VEGF traps referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

25. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

26. Therefore, only the VEGF traps set forth as Flt-1(1-3)-Fc, Flt-1(1-$3_{R>N}$)-Fc, Flt-1(1-$3_{\Delta B}$)-Fc, Flt1(2-$3_{\Delta B}$)-Fc, Flt-1(2-3)-Fc, Flt-1D2-VEGFR3-FcΔC1(a), Flt-1D2-Flk-1D3-FcΔC1(a), and VEGFR1R2-FcΔC1(a), but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, 2nd Paragraph

27. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

28. Claims 1-2, 6, 8-10, 13-15, and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

29. Claims 1, 9, and 15 are rejected as being indefinite for reciting the term "VEGF-mediated activity". Since neither the art nor the specification provides an unambiguous definition of the term, the metes and bounds of the claims cannot be determined.

30. Claims 2 and 10 are rejected as being indefinite for reciting the term "glycemic control". Since neither the art nor the specification provides an unambiguous definition of the term, the metes and bounds of the claims cannot be determined.

31. Claim 15 is further rejected as being indefinite because the claim does not have a step that clearly relates back to the preamble. For example, there is no step indicating that administration of the agent results in improving glucose tolerance or insulin sensitivity.

32. Claims 6, 8, 13-14, and 18-19 are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

33. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

34. Claims 1, 8-9, 14-15, and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Thorpe et al. (U.S. Pat. No. 6,524,583, filed 28 April 2000).

35. Thorpe et al. teach an anti-VEGF antibody that inhibits binding of VEGF to the VEGFR2 receptor and that demonstrates inhibition of VEGF-mediated angiogenesis (i.e., a VEGF-mediated activity) via the VEGFR2 receptor (See column 1, lines 19-23 and column 3, lines 12-21). Thorpe et al. also teach a method for the treatment of undesired angiogenesis associated with diabetes (See column 22, lines 25-40) and teach routes of administration may include transdermal, intramuscular, intravenous, oral, and nasal (See column 25, lines 39-48. It is noted that since claims 1 and 9 recite the limitation of "such that diabetes is treated" without setting forth any specific measure or endpoint of the treatment, the administration of the anti-VEGF antibody for the treatment of diabetes as taught by Thorpe would inherently result in the "treatment" of diabetes. It is further noted that the recitation in claim 15 of "A method of improving glucose tolerance or insulin sensitivity" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable

weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Thus, Thorpe et al. meets all the limitations of claims 1, 8-9, 14-15, and 19.

Summary

36. No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback**, can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JML
October 27, 2005

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER